REMARKS

Claims 1-5, 8-11, and 22-33 are pending in this application. Applicants have amended claims 1, 3-5, 8, 9, and 11, and canceled claims 6, 7, and 12-21 without prejudice or disclaimer. Claims 22-33 are new. Support for the amendments and new claims can be found in the specification, e.g., at page 19, line 22 to page 23, line 38; page 24, line 24 to page 25, line 11; page 4, lines 6-7; and page 6, lines 3-4. No new matter has been added.

Amended claims 1, 3-5, 8, 9, and 11 and new claims 22-33 read on the elected invention and on the elected species.

Information Disclosure Statement

Applicants request that the Office consider the documents cited to the Office in the PTO-1449 form that accompanied the Information Disclosure Statement filed on September 7, 2007, initial the PTO-1449 form, and return a copy of the initialed PTO-1449 form to Applicants.

Objections to the Specification

The Office at page 3 of the Office Action objects to the specification and remarks that lines 1-4 on page 37 recite a sequence identifier (SEQ ID NO:16) that is not disclosed in the sequence listing submitted for this application.

Applicants have amended the specification as indicated herein to recite that the cytochrome c sequence is depicted in SEQ ID NO:8. As described at page 31, lines 22-32, SEQ ID NO:8 is a cytochrome c sequence. Applicants submit that this amendment to the specification does not constitute new matter.

In light of the amendments presented herein, Applicants respectfully request that this objection be withdrawn.

Objections to the Claims

Claim 4. The Office at page 4 of the Office Action objects to claim 4 for the recitation of "the cytochrome c polypeptide is human," because a polypeptide cannot be human.

Applicants have amended the claim as suggested by the Office, and request that this objection be withdrawn.

Claims 6-8. The Office at page 4 of the Office Action objects to claims 6-8 because the abbreviations recited therein should be written out when used for the first time. Claims 6 and 7 have been canceled. Applicants have amended claim 1, and the amendments to claim 1 include a recitation of "Silent Information Regulator (SIR)." Applicants submit that the Office's objection has been overcome by this amendment and request withdrawal of the objection.

Claim 8. The Office at page 4 of the Office Action objects to claim 8 "for containing non-elected subject matter, i.e., SIRT2 and SIRT3."

Applicants respectfully disagree. As indicated in the Restriction Requirement dated October 4, 2006, Applicants were required to elect a species "to which the claims shall be restricted if no generic claim is finally held allowable" (page 3 of the Restriction Requirement). The Requirement went on to state that "Upon allowance of a generic claim, applicant will be entitled to consideration of claims to additional species which are written in dependent form or otherwise include all the limitations of an allowed generic claim" (page 4 of the Restriction Requirement).

The Restriction Requirement also stated that "Claims 1-11 are generic" (*Id.*). Because claims 1 is a generic claim (both in its original and currently amended form), Applicants submit that they should not be required to narrow claim 8 to recite only the elected species, as the full scope of the claim may finally be held allowable. Applicants request that the objection be withdrawn.

Rejection under 35 U.S.C. §112, 1st Par., Written Description

The Office at pages 4-7 of the Action alleges that claims 1-11 lack written description, specifically, that Applicants failed to demonstrate possession of the claimed invention.

Claims 6 and 7 have been canceled, obviating the rejection with respect to those claims.

Applicants respectfully disagree with the Office's position, but in the interest of expediting prosecution, Applicants have amended claims 1, 9, and 11 to recite, in part, that the polypeptide in the claimed methods is "a Silent Information Regulator (SIR) polypeptide having deacetylase activity ... wherein the amino acid sequence of the SIR polypeptide comprises an amino acid sequence that is at least 95% identical to an amino acid sequence of a SIR protein selected from the group consisting of: SIRT1 (SEQ ID NO:1); SIRT2 (SEQ ID NO:2); SIRT3

(SEQ ID NO:3); SIRT4 (SEQ ID NO:4); SIRT5 (SEQ ID NO:5); SIRT6 (SEQ ID NO:6); and SIRT7 (SEQ ID NO:7)."

The amended claims recite a polypeptide with at least 95% identity to a disclosed amino acid sequence and further recite that the polypeptide possesses a function of the polypeptide of the disclosed amino acid sequence (deacetylase activity). Applicants submit that amended claims 1, 9, and 11 are analogous to Example 14 of the Synopsis of Application of Written Description Guidelines ("Guidelines")[1] and thus satisfy the written description requirement. Applicants respectfully request that the written description rejection of amended claims 1, 9, and 11 (and their dependencies, claims 2-5, 8, 10) be withdrawn.

For at least these reasons, Applicants also submit that new claims 22, 23, 27, 28, and 31, which depend from claim 1, 9, or 11, also satisfy the written description standard.

Applicants have added new method claims 24, 29, and 32, which recite, in part, "a SIR polypeptide having deacetylase activity ... wherein the SIR polypeptide comprises an amino acid sequence that is encoded by a nucleic acid that hybridizes under high stringency conditions (hybridizes in 6X SSC at about 45°C, followed by one or more washes in 0.2X SSC, 0.1% SDS at 65°C) to the complement of a nucleic acid encoding an amino acid sequence of a SIR protein selected from the group consisting of: SIRT1 (SEQ ID NO:1); SIRT2 (SEQ ID NO:2); SIRT3 (SEQ ID NO:3); SIRT4 (SEQ ID NO:4); SIRT5 (SEQ ID NO:5); SIRT6 (SEQ ID NO:6); and SIRT7 (SEQ ID NO:7)." As these claims recite a polypeptide that hybridizes under high stringency conditions to a disclosed sequence and that the polypeptide possesses a function of the polypeptide of the disclosed amino acid sequence (deacetylase activity), the claims are similar to Example 9 of the Guidelines. Therefore, Applicants submit that these claims (and their dependencies, claims 25, 26, 30, and 33) satisfy the written description requirement.

Rejection under 35 U.S.C. §112, 1st Par., Enablement

Applicants thank the Office for stating at page 7 of the Office Action that the specification enables an in vitro method of measuring deacetylation activity of human SIRT2 and human SIRT3 of SEQ ID NOS:2 and 3, respectively, on chemically acetylated cytochrome c polypeptides.

At pages 7-13 of the Office Action, the Office alleges that claims 1-11 are not enabled.[2]

Claims 6 and 7 have been canceled, obviating the rejection with respect to these claims.

Applicants respectfully disagree with the Office's position. However, in the interest of advancing prosecution, Applicants have amended claims 1, 9, and 11. As described above, the amended claims recite, in part, that the polypeptide in the claimed methods is "a Silent Information Regulator (SIR) polypeptide having deacetylase activity ... wherein the amino acid sequence of the SIR polypeptide comprises an amino acid sequence that is at least 95% identical to an amino acid sequence of a SIR protein selected from the group consisting of: SIRT1 (SEQ ID NO:1); SIRT2 (SEQ ID NO:2); SIRT3 (SEQ ID NO:3); SIRT4 (SEQ ID NO:4); SIRT5 (SEQ ID NO:5); SIRT6 (SEQ ID NO:6); and SIRT7 (SEQ ID NO:7)." Applicants submit that these amended claims are enabled because a skilled practitioner could practice the claimed methods without undue experimentation.

As part of its rejection, the Office alleges:

> [T]he disclosure of an in vitro method of measuring deacetylation activity of human SIRT2 and human SIRT3 comprising the amino acid sequence as set forth in SEQ ID NOs:2 and 3, respectively, on chemically acetylated cytochrome c polypeptides does not commensurate with the breadth of claimed methods encompassing the use of all possible "polypeptides having acetylase or deacetylase activity or any fragment thereof" optionally expressed in any cell. (Office Action at page 10)

Applicants respectfully point out that the specification provides working examples demonstrating that each of SIRT1, SIRT2, SIRT3, SIRT5, SIRT6, and SIRT7 deacetylate cytochrome c. See, e.g., Example 4 on page 72, "Cell Derived SIRT1-7 Deacetylation Activity on Cytochrome C" and the results shown in Figure 4. Further, the amended claims recite a Silent Information Regulator (SIR) polypeptide having deacetylase activity and at least 95% identity to one of seven disclosed amino acid sequences. A skilled practitioner could identify and/or prepare such polypeptides using the teachings provided in the specification. For example, the specification provides ample teachings regarding SIR polypeptides, how to identify a SIR polypeptide, and examples of the amino acid sequences of representative SIR polypeptides and conserved regions of SIR polypeptides. See, e.g., page 19, line 22 to page 30, line 7.

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[1] The guidelines are available at http://www.uspto.gov/web/menu/written.pdf.

[2] Applicants note that on page 7 of the Office Action, the Office states claims 1-7 were rejected, yet at page 9 it indicates that claims 1-11 were rejected. Applicants assume that the Office is rejecting claims 1-11.

Further, with respect to the cell used in the claimed methods, the Office states, "It is noted by the Examiner that the recitation of 'a cell which expresses …' in claims 9 and 11 encompasses the use of transgenic animal or plants, which is not supported or disclosed in the instant application" (Office Action at page 11).

Applicants disagree and point out that the specification does indeed disclose the use of transgenic organisms. For example, as stated on page 38, lines 9-12:

> Some exemplary screening assays for assessing activity or function include one or more of the following features:
> use of a transgenic cell, e.g., with a transgene encoding a polypeptide having acetylation or deacetylation activity and/or a cytochrome c polypeptide or mutants thereof …

Further, page 50, line 23 to page 51, line 8 recite:

> In addition to cell-based and in vitro assay systems, non-human organisms, e.g., transgenic non-human organisms, can also be used. A transgenic organism is one in which a heterologous DNA sequence is chromosomally integrated into the germ cells of the animal. A transgenic organism will also have the transgene integrated into the chromosomes of its somatic cells. Organisms of any species, including, but not limited to: yeast, worms, flies, fish, reptiles, birds, mammals (e.g., mice, rats, rabbits, guinea pigs, pigs, micro-pigs, and goats), and non-human primates (e.g., baboons, monkeys, chimpanzees) may be used in the methods of the invention.
> A transgenic cell or animal used in the methods of the invention can include a transgene that encodes, e.g., a copy of a polypeptide having acetylation or deacetylation activity and/or cytochrome c, e.g., a polypeptide having acetylation or deacetylation activity or cytochrome c polypeptide that was evaluated for an interaction with the test compound. The transgene can encode a protein that is normally exogenous to the transgenic cell or animal, including a human protein, e.g., a human SIR polypeptide and/or human cytochrome c. The transgene can be linked to a heterologous or a native promoter. Methods of making transgenic cells and animals are known in the art.

Page 53, line 7 to page 57, line 2 provides a description of how to perform assays in model organisms and sets forth examples of model organisms for human diseases.

Additional examples can be found at page 7, line 10 to page 8, line 21 of the specification. Thus, the use of transgenic cells or animals is supported throughout the specification. Further, the specification also provides a detailed description of additional cells that can be used to practice the invention. For example, as stated at page 49, line 17 to page 50, line 22:

> In another embodiment, the assay, e.g., the assay for selecting compounds which interact with a polypeptide and/or which effect (e.g., induce) apoptosis, can be a cell-based assay. The cell based assay can include contacting a cell expressing a polypeptide having acetylation or deacetylation activity and/or cytochrome c with a test compound and determining the ability of the test compound to modulate (e.g. stimulate or

inhibit) an activity of the polypeptide or cytochrome c, and/or determine the ability of the test compound to modulate polypeptide and/or cytochrome c expression, e.g., by detecting nucleic acids (e.g., mRNA or cDNA) or proteins in the cell. A preferred activity is the deacetylation function of a polypeptide of cytochrome c; a further preferred activity is the ability to cause apoptosis. Determining the ability of the test compound to modulate the activity of a polypeptide can be accomplished, for example, by determining the ability of a polypeptide to bind to or interact with the test molecule, and by determining the ability of the test molecule to stimulate apoptosis. Cell-based systems can be used to identify compounds that decrease the polypeptides expression and/or activity and/or effect, e.g., decrease or prevent apoptosis, or visa versa. Such cells can be recombinant or non-recombinant, such as cell lines that express the gene encoding the polypeptide and/or the cytochrome c gene. In some embodiments, the cells can be recombinant or non-recombinant cells which express a transcription factor. Preferred systems are mammalian or yeast cells that express a polypeptide having acetylation or deacetylation activity and cytochrome c. In utilizing such systems, cells are exposed to compounds suspected of decreasing expression of a deacetylating polypeptide and/or decreasing deacetylation activity of the polypeptide and/or reducing apoptosis, or compounds suspected of increasing expression of a deacetylating polypeptide and/or increasing a deacetylation activity and/or inducing apoptosis. After exposure, the cells are assayed, for example, for expression of the gene or activity of the protein. Alternatively, the cells may also be assayed for the inhibition of the deacetylation function of a polypeptide, or the apoptotic or cytostatic function. In one embodiment, the visual assessment can be used for evidence of apoptosis, e.g., nuclear fragmentation.

Another preferred cell for a cell-based assay comprises a yeast cell transformed with a vector comprising the Sir2 gene, a homolog of human a SIRT1. One use for a yeast cell expressing Sir2 is to mutagenize the yeast and screen for yeast that will survive only when the Sir2 polypeptide is functioning normally. Synthetic lethal screens are described in Holtzman et al. (1993), J. Cell Bio. 122: 635-644. The yeast that require Sir2 function for survival can then be used to screen test compounds for those that inhibit Sir2 activity. Test compounds that results in a decrease in yeast survival are likely inhibitors of Sir2 in this system.

A cell used in the methods of the invention can be from a stable cell line or a primary culture obtained from an organism, e.g., a organism treated with the test compound.

Further, the specification provides numerous examples of other types of cells that can be used in practicing the claimed methods. Examples of cells that can be used and examples of how to use the cells are provided, e.g., at page 3, lines 4-8; page 4, line 15 to page 5, line 5; page 6, lines 8-29; page 7, line 10 to page 8, line 21; page 9, lines 1-7; page 10 line 23 to page 13, line 26; page 17, lines 3-8. Page 30, lines 9-13 states:

A "purified preparation of cells", as used herein, refers to an in vitro preparation of cells. In the case cells from multicellular organisms (e.g., plants and animals), a purified preparation of cells is a subset of cells obtained from the organism, not the entire intact organism. In the case of unicellular microorganisms (e.g., cultured cells and microbial cells), it consists of a preparation of at least 10% and more preferably 50% of the subject cells. (emphasis added)

Thus, the full scope of the cell recited in claims 9 and 11 (and their dependencies) is enabled by the specification. Applicants submit that in light of the ample teachings of the specification, a skilled practitioner could practice the invention of claims 1, 9, and 11 (and their dependencies, claims 2-5, 8, 10) without undue experimentation and request that this rejection be withdrawn.

For at least these reasons, Applicants also submit that new claims 22, 23, 27, 28, and 31, which depend from claim 1, 9, or 11, are also enabled.

New claims 24, 29, and 32 (and their dependencies, claims 25, 26, 30, and 33) recite, in part, "a SIR polypeptide having deacetylase activity ... wherein the SIR polypeptide comprises an amino acid sequence that is encoded by a nucleic acid that hybridizes under high stringency conditions (hybridizes in 6X SSC at about 45°C, followed by one or more washes in 0.2X SSC, 0.1% SDS at 65°C) to the complement of a nucleic acid encoding an amino acid sequence of a SIR protein selected from the group consisting of: SIRT1 (SEQ ID NO:1); SIRT2 (SEQ ID NO:2); SIRT3 (SEQ ID NO:3); SIRT4 (SEQ ID NO:4); SIRT5 (SEQ ID NO:5); SIRT6 (SEQ ID NO:6); and SIRT7 (SEQ ID NO:7)."

Because these claims recite polypeptides that hybridize under high stringency conditions to a disclosed sequence and the polypeptides possess a function of the disclosed amino acid sequence (deacetylase activity), and because the specification provides ample guidance on how to perform hybridization experiments and how to test proteins (see, e.g., page 24, line 24 to page 25, line 11; page 26, line 22 to page 27, line 10), Applicants submit that claims 24, 29, and 32 (and their dependencies, claims 25, 26, 30, and 33) are enabled. Indeed, a skilled practitioner could practice the claimed methods without undue experimentation.

CONCLUSION

For at least the reasons stated above, Applicants respectfully submit that all pending claims are in condition for allowance, which action is expeditiously requested. Applicants do not concede any positions of the Examiner that are not expressly addressed above, nor do Applicants concede that there are not other good reasons for patentability of the presented claims or other claims.

If this response is not considered timely filed and if a request for an extension of time is otherwise absent, Applicant hereby requests any necessary extension of time. Please charge any deficiency to Deposit Account No. 50/2762.

Respectfully submitted,
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